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Supplementary Information for *Mapping global sensitivity of cellular network dynamics: sensitivity heat maps and a global summation law*.

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1 INTRODUCTION

This is supplementary information for the paper *Mapping global sensitivity of cellular network dynamics: sensitivity heat maps and a global summation law.* by D. A. Rand. The latter paper is referred to henceforth as **I**.

Suppose that the differential equation being considered is written as $\dot{x} = f(t, x, k)$ where $x \in \mathbb{R}^n$ and the the set of parameters $k_1, \ldots, k_s$ is collected together into a parameter vector $k \in \mathbb{R}^s$. The systems may depend upon other parameters but for the discussion here we assume that these other parameters are held fixed and only $k_1, \ldots, k_s$ are varied. As in **I** we introduce scaled parameters $\eta_i = \log k_i$.

Suppose that the solutions of interest, which depends upon the parameters k is given by $x(t) = g(t, k)$. Here we will concentrate on two types of dynamic solutions: periodic oscillations (i.e. limit cycles) and transcient signals. By the latter we mean solutions $x(t) = g(t, k)$ of the equation $\dot{x} = f(t, x, k)$ with a given initial condition $x_0 = g(0, k)$. The system starts in a given state x_0 and is subject to a given perturbation caused by an incoming signal that is modeled in the time dependence of the right-hand side $f(t, x, k)$ of the differential equation.

Suppose that we denote the solution of the differential equation with initial condition x and parameters k by $\xi(t, x, k)$. To determine the derivatives $\partial\xi/\partial x_i$ and $\partial\xi/\partial k_j$ we consider the variational equation

$$\frac{\partial}{\partial t} X(s, t) = J(t) \cdot X(s, t) \tag{1}$$

where $J(t)$ is the Jacobian $d_x f$ evaluated at $x = g(t, k)$, $X(s, t)$ is a $n \times n$ matrix and the initial condition is $X(s, s) = I$. We denote $X(0, t)$ by $X(t)$. Then the jth column of $X(t)$ is $\partial\xi/\partial x_j$ evaluated at $(t, g(t), k)$.

To determine partial derivatives with respect to parameters we consider the associated equation

$$\dot{Y}(t) = J(t) \cdot Y(t) + K_j(t) \tag{2}$$

where $K_j(t)$ is the n-dimensional vector $\partial f/\partial k_j$ evaluated at $x = g(t)$, Y is a $n \times s$ matrix and the initial condition is $Y(0) = 0$. Then

$$Y(t) = \frac{\partial\xi}{\partial k_j}(t, g(t), k).$$

If $X(s, t)$ is the solution of (1) then by variation of constants,

$$\frac{\partial\xi}{\partial k_j}(t, g(t), k) = \int_0^t X(s, t) K_j(s)\, ds. \tag{3}$$

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It is also proved in [1] p. 417 that if f does not depend explicitely on t (i.e. the equation is autonomous) then $X(s, t) \cdot f(g(s), k) = f(g(t), k)$.

2 CALCULATING THE U_I

We restrict time t to a discrete set of values $t_1, \ldots, t_N$ and for each parameter k_j and each state variable x_m consider the column vectors $r_{m,j} = (\delta g_m/\delta\eta_j(t_1), \ldots, \delta g_m/\delta\eta_j(t_N))$. For each j we concatenate these into a single column vector r_j and then consider the matrix M whose jth column is r_j.

This matrix is a time-discretised version of the linear operator $\mathbf{M}$ that associates to each change of scaled parameters $\delta\eta = (\delta\eta_i, \ldots, \delta\eta_s)$ the change δg in the solution of interest g which is in the infinite-dimensional space of appropriate n-dimensional time-series. Thus $\delta g = \mathbf{M} \cdot \delta\eta \approx M \cdot \delta\eta$ and $\partial g/\partial\eta_j = \mathbf{M} \cdot e_j \approx M \cdot e_j$ where e_j is the vector all of whose entries are zero except for the jth which is 1. We therefore call M a *discretised derivative matrix*. If the solution g is scaled as in section 2.4 of **I** then M is scaled accordingly.

For mutidimensional functions $x(t) = (x_1(t), \ldots, x_n(t))$ such as $g(t)$ and $\delta g_j/\delta\eta_i(t)$ above on the time interval $0 \leq t \leq T$, we measure their size using the norm $\|x\|^2 = \sum_m \int_0^T \|x(t)\|^2$. It follows from this that, in the case where the time steps $\Delta t_i = t_{i+1} - t_i$ are independent of i the σ_i and $U_i(t)$ of the fundamental observations are approximated by the the singular value decomposition (SVD) of the matrix $M_1 = \sqrt{\Delta t/T} M$ [2]. The normalisation by $\sqrt{\Delta t/T}$ is chosen to ensure that asymptotically (as $N \to \infty$) the SVD of M is independent of the choice of the time discretisation. It follows from the choice of norm $\|\cdot\|$ above. In the case where they do depend on i take $M_1 = T^{-1} M\delta$ where Δ is the diagonal matrix whose components are the numbers $\sqrt{\Delta t_i}$.

We use the version of SVD that is often called thin SVD. Since M_1 has N rows and s columns (i.e. is $N \times s$) this SVD is a decomposition into a product of the form $M = UDV^t$ where U is a $N \times s$ orthonormal matrix ($UU^t = I_N$ and $U^t U = I_s$), V is a $s \times s$ orthonormal matrix and $D = diag(\sigma_1, \ldots, \sigma_s)$ is a diagonal matrix. The elements $\sigma_1 \geq \cdots \geq \sigma_s$ are the *singular values* of M. The matrix W of **I** is the inverse of V and since V is orthogonal $W = V^t$.

The columns V_j of V provide an orthonormal basis for the parameter space: $(V_j \cdot V_k = \delta_{jk})$. Any change $\delta\eta$ of parameters can be written in this basis as $\delta\eta = \sum_i \lambda_i V_i$ where the new coordinates λ_i are given by $\lambda = V^{-1} \cdot \delta\eta = W \cdot \delta\eta$.

The columns U_j of U provide an orthonormal basis for the space of discretised time-series. As for r_j they are in the concatenated form. To restore them to their form as time-series in n-dimensional space, the concatenation must be undone but this is straightforward. The $U_j(t_i)$ then approximate the $U_j(t)$. From $M = UDV^t$ one immediately deduces that $M \cdot V_j = \sigma_j U_j$. The fundamental equation (2) of **I** follows directly from this because

$$\delta g \approx M \cdot \delta\eta + O(||\delta\eta||^2) = \sum_i \lambda_i \sigma_i U_i + O(||\delta\eta||^2).$$

We note that since all the partial derivatives of g are bounded the results are effectively independent of the choice of N provided it is chosen large enough and therefore we have that, for large N,

$$\partial g/\partial\eta_j = M \cdot e_j. \tag{4}$$

But $e_j = \sum_i W_{ij} V_i$ and therefore

$$\begin{aligned} \partial g/\partial\eta_j &= \sum_i M \cdot W_{ij} V_i = \sum_i W_{ij} M \cdot V_i \\ &= \sum_i W_{ij} \sigma_i U_i = \sum_i S_{ij} U_i. \end{aligned} \tag{5}$$

3 AUTONOMOUS OSCILLATORS

In this section we consider limit cycles of autonomous systems of the form $\dot{x} = f(x, k)$ (i.e. where f does not depend explicitely on t). The limit cycle is given by $g(t, k)$ and $x_0(k) = g(0, k)$ is its initial condition. We will make an innocent assumption on the choice of the initial condition $x_0(k) = g(0, x, k)$. We assume that as k is varied near to k_0, $x_0(k)$ varies in a small $(n-1)$-dimensional hyperplane Σ which intersects the the periodic orbit $g(t, k_0)$ in a single point and is transversal to the periodic orbit. (We could instead make the following weaker assumption: assume that as k is varied near to k_0, if $x_0(k) = g(t, x, k_0)$ for some t then $x_0(k) = x_0(k_0)$.) The former condition is a weak one since if Σ is any such $(n-1)$-dimensional hyperplane which intersects the the periodic orbit $g(t, k_0)$ transversally and if we choose $x_0(k)$ to be the unique point where the periodic orbit for k meets Σ, then it satifies the condition.

Since the period $\tau = \tau(k)$ of g can change with the parameters, $\partial g/\partial k_j$ is not a periodic function of time in general. However, if $\gamma(t, k) = g(\bar{\tau} t, k)$ where $\bar{\tau} = \tau(k)/\tau(k_0)$ then $\partial\gamma/\partial k_j$ is periodic with period $\tau_0 = \tau(k_0)$, because this is the period of γ which is independent of k. But

$$\frac{\partial\gamma}{\partial k_j} = \tau_0^{-1} t \frac{\partial\tau}{\partial k_j}\frac{\partial g}{\partial t} + \frac{\partial g}{\partial k_j} = \tau_0^{-1} t \frac{\partial\tau}{\partial k_j} f(g) + \frac{\partial g}{\partial k_j}.$$

Thus we deduce that $\partial g/\partial k_j$ can be written as $p_1(t) + tp_2(t)$ where p_1 and p_2 are periodic functions with period τ_0 and $p_2(t) = (\partial\tau/\partial k_j) f(g)$. But then

$$\begin{aligned} \frac{\partial g}{\partial k_j}(t+\tau_0) \quad &- \quad \frac{\partial g}{\partial k_j}(t) = \tau_0 p_2(t) \\ &= \quad (\partial\tau/\partial k_j) f(g(t, k_0)). \end{aligned}$$

Since $\partial g/\partial k_j(0) = 0$,

$$\frac{\partial g}{\partial k_j}(\tau_0) = (\partial\tau/\partial k_j) f(g(t, k_0))$$

and we deduce that the derivative of period τ is given by

$$\frac{\partial\tau}{\partial k_j} = \frac{1}{f_m(x_0)}\frac{\partial g_m}{\partial k_j}(\tau_0) \tag{6}$$

for all m.

4 SUMMATION LAW

We again consider systems of the form $\dot{x} = f(t, x, k)$. The assumption about the parameters k is that the set of parameters being considered is a full set of linear parameters $k_1, \ldots, k_s$. These are the parameters in front of each term in f and it is further assumed that there is a linear parameter in front of each term in f so that $f(t, x, \rho k) = \rho f(t, x, k)$ for all $\rho > 0$.

The following equation (7), which we prove in sections 4.1 and 4.2, is the basis of our main summation law:

$$\sum_j k_j \frac{\partial\xi}{\partial k_j}(t, x_0, k) = \Phi(t) \tag{7}$$

where

$$\Phi(t) = tf(t, g(t), k) - \int_0^t sX(s, t) \cdot \frac{\partial f}{\partial t}(t, g(t), k)\, ds.$$

In the case where the equation is autonomous (i.e. f does not depend explicitely on time t) the term under the integral is zero and $\Phi(t) = tf(g(t), k)$. Other summation laws for such systems will be discussed in [3].

4.1 Autonomous systems

For autonomous systems of the form $\dot{x} = f(x, k)$. this result follows from the fact that since $f(x, \rho k) = \rho f(x, k)$ for all $\rho > 0$,

$$\xi(t, x_0(k), \rho k) = \xi(\rho t, x_0(k), k) \tag{8}$$

and therefore (7) follows by applying Euler's theorem.

4.2 Forced systems

We now consider systems of the form $\dot{x} = f(t, x, k)$. The assumption about the parameters k is that $f(t, x, \rho k) = \rho f(t, x, k)$ for all $\rho > 0$.

We can rewrite this as an autonomous system by defining $y = (s, x) \in \mathbb{R} \times \mathbb{R}^n$ and letting $F(y) = (\omega, f(s, x, k))$ where ω is a new parameter that we introduce. Then the equation

$$\dot{y} = F(y) \tag{9}$$

is equivalent to

$$\begin{aligned} \dot{s} &= \omega \\ \dot{x} &= f(s, x, k) \end{aligned}$$

and therefore, since this implies $s = \omega t$, we have that x satisfies

$$\dot{x} = f(\omega t, x, k) \tag{10}$$

which for $\omega = 1$ is our original equation. We denote the solution of (10) by $\xi_\omega(t, x_0, k)$ (x_0 the initial condition) and the solution of (9) by $\Xi(t, y_0, k)$.

The set of parameters ω, k is a full set of linear parameters for equation (9) and this equation is autonomous. Therefore, we can apply the result proved above (using the initial condition $y_0 =$

$(0, x_0)$) to deduce that

$$\omega \frac{\partial \Xi}{\partial \omega}(t, y_0, k) + \sum_j k_j \frac{\partial \Xi}{\partial k_j}(t, y_0, k) = tF(y(t)) \quad (11)$$

and $y(t) = \Xi(t, y_0, k) = (\omega t, \xi_\omega(t, x_0, k))$. But

$$\frac{\partial \Xi}{\partial \omega}(t, y_0, k) = (t, \frac{\partial \xi_\omega}{\partial \omega}(t, x_0, k))$$

and

$$\frac{\partial \Xi}{\partial k_j}(t, y_0, k) = (0, \frac{\partial \xi_\omega}{\partial k_j}(t, x_0, k)).$$

Evaluating these at $\omega = 1$ and substituting them into equation (11) we deduce that

$$\begin{aligned} \sum_j k_j \frac{\partial \Xi}{\partial k_j}(t, y_0, k) &= tF(y(t)) - \frac{\partial \Xi}{\partial \omega}(t, y_0, k) \\ = (t, f(\xi(t, x_0, k)) &- (t, \left.\frac{\partial \xi_\omega}{\partial \omega}\right|_{\omega=1}(t, x_0, k)) \\ = (0, f(\xi(t, x_0, k)) &- \left.\frac{\partial \xi_\omega}{\partial \omega}\right|_{\omega=1}(t, x_0, k)). \end{aligned}$$

However, by the above results in section 1,

$$\left.\frac{\partial \xi_\omega}{\partial \omega}\right|_{\omega=1}(t, x_0, k) = \int_0^t X(s, t) \cdot s \frac{\partial f}{\partial t}(s, g(s), k)\, ds.$$

since $g(t) = \xi_1(t, x_0, k)$ and the derivative of the right-hand side of (10) with respect to ω is $t\partial f/\partial t$. Thus we deduce that

$$\sum_j k_j \frac{\partial \xi}{\partial k_j}(t, x_0, k) = \Phi(t). \quad (12)$$

4.3 Case of transcient signals

In the case where the solution $g(t, k)$ is defined by its initial condition $g(0, k) = x_0$. Then, the C_i are determined as above with $\partial g/\partial k_j(t) = \partial \xi/\partial k_j(t, x_0, k)$. Therefore, by equations (5) and (7)

$$\begin{aligned} \sum_{i,j} W_{ij} C_i(t) &= \sum_j \frac{\partial g}{\partial \eta_j}(t) \\ &= \sum_j \frac{\partial \xi}{\partial \eta_j}(t, x_0, k) = \Phi(t) \quad (13) \end{aligned}$$

4.4 Case of limit cycles

4.4.1 Autonomous systems We firstly consider the autonomous case. Notation and assumptions are as in section 3.

We have seen that since $f(x, \rho k) = \rho f(x, k)$ for all $\rho > 0$,

$$\xi(t, x_0(k), \rho k) = \xi(\rho t, x_0(k), k). \quad (14)$$

Applying this to the case where $t = \tau(k)$ the period of the limitcycle and where $x_0(k)$ is the initial condition as in section 3 we deduce that

$$\tau(\rho k) = \rho^{-1} \tau(k)$$

and hence that

$$\sum_j k_j \frac{\partial \tau}{\partial k_j} = -\tau. \quad (15)$$

Moreover, (14) implies that $x_0(k) = x_0(\rho k)$ because this is where both $\xi(t, x_0, k)$ and $\xi(t, x_0, \rho k)$ intersect Σ for $t > 0$. Therefore,

$$\sum_j k_j \frac{\partial x_0}{\partial k_j} = 0. \quad (16)$$

Since $g(t, k) = \xi(t, x_0(k), k)$,

$$\sum_j k_j \frac{\partial g}{\partial \eta_j} = \frac{\partial \xi}{\partial x_0} \cdot \sum_j k_j \frac{\partial x_0}{\partial k_j} + \sum_j k_j \frac{\partial \xi}{\partial k_j} \quad (17)$$

where all derivatives etc are evaluated at t, x_0 and k_0. But the first term on the left-hand side is zero by (15) and the second equals $tf(g(t, k))$ by (**??**). Thus,

$$\sum_j k_j \frac{\partial g}{\partial k_j}(t) = tf(g(t, k)) = \Phi(t). \quad (18)$$

Note that $tf(g(t, k)) = t\dot{g}(t, k_0)$ which is an infinitesimal period change (i.e. the derivatative at $\omega = 1$ of $\omega \to g(\omega t)$).

Now we note the following form of the summation theorem for periodic orbits of automomous systems. Let $\gamma(t, k) = g(\bar{\tau} t, k)$ as above in section 3. Then γ is periodic in t with period $\tau_0 = \tau_{k_0}$. The summation theorem for γ is

$$\sum_j k_j \frac{\partial \gamma}{\partial k_j} = 0. \quad (19)$$

Proof. Since

$$\gamma(t, k) = \xi(\bar{\tau} t, x_0(k), k) = \xi(t, x_0(k), \bar{\tau} k)$$

it follows that

$$\frac{\partial \gamma}{\partial k_j} = \frac{\partial \xi}{\partial x_0} \frac{\partial x_0}{\partial k_j} + \bar{\tau} \frac{\partial \xi}{\partial k_j} + \frac{\partial \bar{\tau}}{\partial k_j} \sum_i k_i \frac{\partial \xi}{\partial k_i}.$$

Thus

$$\begin{aligned} \sum_j k_j \frac{\partial \gamma}{\partial k_j} &= \frac{\partial \xi}{\partial x_0} \sum_j k_j \frac{\partial x_0}{\partial k_j} + \bar{\tau} \sum_j k_j \frac{\partial \xi}{\partial k_j} \\ &\quad + \sum_j k_j \frac{\partial \bar{\tau}}{\partial k_j} \sum_i k_i \frac{\partial \xi}{\partial k_i} \\ &= 0 \end{aligned}$$

by equations (15) and (16).

4.4.2 Forced systems Now we consider the non-autonomous equation $\dot{x} = f(t, x, k)$. We assume that f is of period τ in the sense that $f(t + \tau, x, k) \equiv f(t, x, k)$ and suppose that $x = g(t, k)$ is a periodic solution with period τ. We assume that this solution is non-degenerate in the sense that 1 is not an eigenvalue of $X(\tau)$.

Let $y(t) = \sum_j k_j \partial g/\partial k_j(t)$. Since the period τ is independent of k for k near k_0, the derivatives $\partial g/\partial k_j$ are periodic in time with period τ and therefore $y(t)$ also has period τ. Moreover, $y(t)$ is a solution of the equation $\dot{y} = J(t) \cdot y + K(t)$ where $J(t)$ is as in section 1 and $K(t) = \sum_j k_j \partial f/\partial k_j(t)$. The general solution of this equation is

$$y(t) = X(t) \cdot c + \int_0^t X(s,t) \cdot K(s)\, ds$$

for some vector c. Here $X(t)$ and $X(s,t)$ are as in section 1. But the last term equals $\sum_j k_j \partial \xi/\partial k_j(t)$ where ξ is as in section 1 and by equation (7) (see also (12)) this is $\Phi(t)$.

If $y(t) = \sum_j k_j \partial g/\partial k_j(t)$, $y(\tau) = y(0)$ and therefore, since $X(0)$ is the identity, we deduce that $(I - X(\tau))c = \Phi(\tau)$. Since 1 is not an eigenvalue of $X(\tau)$, $(I - X(\tau))$ is invertible and $c = (I - X(\tau))^{-1}\Phi(\tau)$. Therefore,

$$\sum_j k_j \frac{\partial g}{\partial k_j}(t) = X(\tau)(I - X(\tau))^{-1}\Phi(\tau) + \Phi(t). \qquad (20)$$

5 CLASSICAL CONTROL COEFFICIENTS

5.1 Changes in phases and peak times

Suppose that $t = \phi(k)$ is the time when g_m has a minimum or maximum value. Then $\phi(k)$ satisfies $\dot{g}_m(\phi(k), k) = 0$. Therefore, differentiating this wrt k_j we see that

$$\ddot{g}_m(\phi) \cdot \frac{\partial \phi}{\partial k_j} + \frac{\dot{g}_m \phi}{\partial k_j}(\phi) = 0.$$

and hence deduce that

$$\begin{aligned} \frac{\partial \phi}{\partial k_j} &= -\left(\frac{\partial \dot{g}_m}{\partial k_j}(\phi)\right) / \ddot{g}_m(\phi) \\ &= -\left(\left.\frac{\partial}{\partial t}\right|_{t=\phi} \frac{\partial g_m}{\partial k_j}\right) / \ddot{g}_m(\phi) \\ &= -\left(\sum_i S_{ij} \dot{U}_{i,m}(\phi)\right) / \ddot{g}_m(\phi) \qquad (21) \end{aligned}$$

Note that this could have been written in terms of $U_{i,m}$ instead of $\dot{U}_{i,m}$ by using the fact that $(\partial g_m/\partial k_j)^{\cdot} = J(\phi) \cdot (\partial g_m/\partial k_j)$ to deduce that $\left(\sum_i S_{ij} \dot{U}_{i,m}\right) = J(\phi) \cdot \left(\sum_i S_{ij} U_{i,m}\right)$.

5.2 Amplitude

The maximum value M_m of $x_m(t)$ is given by

$$M_m = g_m(t_m(k), k), \qquad \dot{g}_m((t_m(k), k).$$

Differentating wrt k_j gives

$$\begin{aligned} \frac{\partial M_m}{\partial k_j} &= \dot{g}_m(t_m)\frac{\partial t_m}{\partial k_j} + \frac{\partial g_m}{\partial k_j}(t_m) \\ &= \frac{\partial g_m}{\partial k_j}(t_m) \end{aligned}$$

because $\dot{g}_m(T_m) = 0$. Similarly for the minimum value m_m. The formula for amplitude A_m follows from the fact that $A_m = M_m - m_m$.

The α-decrease time $t_{\alpha,m}$ is given by $g_m(t_{\alpha,m}(k), k) - \alpha g(t_m(k), k) = 0$. Differentiating wrt k_j and solving for $\partial t_{\alpha,m}/\partial k_j$ gives

$$\frac{\partial t_{\alpha,m}(k)}{\partial k_j} = \left(\alpha \frac{\partial g_m}{\partial k_j}(t_{\alpha,m}) - \frac{\partial g_m}{\partial k_j}(t_m)\right) / \dot{g}(t_{\alpha,m})$$

6 OPTIMALITY OF S

If S_{ij} has its usual meaning and the $U_{i,m}(t)$ are as in the Fundamental Observation then let $U(t)$ denote the $s \times n$ matrix whose ith row is the n-dimensional vector $U_i(t)$. (Here, as above, n is the dimension of the x-state space.) Then

$$\frac{\partial g}{\partial \eta}(t) = S^t U(t)$$

so that

$$\frac{\partial g_m}{\partial \eta}(t) = S^t U(:, m)(t)$$
$$\frac{\partial g_m}{\partial \eta_j}(t) = S(:, j)^t U(t)$$

and

$$\frac{\partial g_m}{\partial \eta_j}(t) = S(:, j)^t U(:, m)(t) = \sum_i S_{ji} U_{im}(t)$$

Consider the subspace spanned by the functions given by $\partial g/\partial \eta_j(\cdot)$ on $0 \le t \le T$. Assume these vectors are independent so that the subspace is s dimensional. Let $U_i(\cdot)$ be any orthonormal basis of this space. Then $\partial g/\partial \eta(t) = S^t U(t)$ for some matrix S. The U and S coming from the Fundamental observation have the property that they maximise the decay rate of the quantities $\sigma_i^2 = ||S(:, i)||^2$ amongst all such U and S.

7 THE RELATIONSHIP BETWEEN S AND THE FISHER INFORMATION MATRIX

We consider the case where we are fitting a network model described by the equation $\dot{x} = f(t, x, k)$ to data. Each of the state variables x_m in the model corresponds to a particular elementary product of the biological system. We assume that we have experimental time-series $D_{m,\ell}$ for the products $g_m(t_\ell)$ of (i.e. measured values $D_{m,\ell}$ of $g_m(t_\ell)$ for some for some times t_ℓ).

We suppose that we use these data to estimate the parameters of the equation using least squares or some similar error minimisation or likelihood maximisation scheme. Thus we seek to adjust parameters so as to minimise $H = \sum_m \sum_\ell \left(g_m(t_\ell) - D_{m\ell}\right)^2 / \Sigma_m^2$.

Assume that $\eta^* = (\eta_1^*, \ldots, \eta_s^*)$ is the parameter value minimising H. If the times are $t_1, \ldots, t_N$ are such that the spacing $\Delta t = t_{\ell+1} - t_\ell$ is independent of ℓ and if $T_\ell = (t_N - t_1)/\Delta t$,

$$H(g^* + \delta g^*) = \sum_m T_\ell^{-1} \sum_\ell (g_m^*(t_\ell) + \delta g_m^*(t_\ell) - D_{m,l})^2.$$

In the mean $\delta g_q^*(t_\ell)(g_q^*(t_\ell) - D_{q,l}) \approx 0$ and therefore

$$\begin{aligned} H(g^* + \delta g^*) &= H(g^*) + \sum_q T_\ell^{-1} \sum_\ell \delta g_g^*(t_\ell)^2 \\ &\approx H(g^*) + \|\delta g\|. \end{aligned}$$

Table 1. This table lists some key observables for oscillators and signalling systems and gives the expressions in terms of the $U_{i,m}$ for their control coefficients using the formula (5) of the main paper **I**. Most of these formulas are demonstrated in section 5. For free running oscillators the observable considered is period τ. The partial derivative $\partial\tau/\partial\eta_j$ follows from equation (6). We also note that, for an appropriate definition of phase change for free-running oscillators φ, $C_j^{\varphi} = -C_j^{p}$. For forced oscillators the period is constant if the system is entrained but the phase $\varphi^{(m)}$ of each variable $x_m(t)$ can change as parameters vary and we consider these. The amplitude A_m of $x_m(t)$ is the difference between the maximum and minimum values of $x_m(t)$. For signalling systems, I have in mind the case where an incomingF signal S activates a network that was in a steady state. As a result a time-dependent signal $x(t) = (x_1(t), \ldots, x_n(t))$ propagates through the network. We consider the time for the signals to reach their peaks and the α-decrease time. This is the time $t = t_{\alpha,m}$ when the signal $g_m(t)$ has decreased from its peak value $g_m(T_m)$ by a factor α i.e. $g_m(t) = \alpha g(T_m)$.

C_j^Q in terms of eqn. (5) of **I**	t_ℓ	a_ℓ
Oscillators		
free-running period τ	τ	$1/f_m(x_0)$
Forced oscillators		
phase Φ_m of variable m's max.	Φ_m	$-1/g''_m(\Phi_m)$
phase ϕ_m of variable m's min.	ϕ_m	$-1/g''_m(\phi_m)$
amplitude A_m of variable m	Φ_m, ϕ_m	1, -1
Signalling systems		
time $t_{m,\ell}$ for x_m to reach ℓth peak	$t_{m,\ell}$	$-1/x''_m(t_{m,\ell})$
α-decrease time $t_{\alpha,m}$	$T_m, t_{\alpha,m}$	$\alpha/g'_m(t_{\alpha,m})$, $-1/g'_m(t_{\alpha,m})$

But since $\delta g = \sum_i \lambda_i \sigma_i U_i$,

$$\begin{aligned} \|\delta g\| &= \sum_i \lambda_i^2 \sigma_i^2 = \lambda^t D^2 \lambda \\ &= \delta\eta^t W^t D^2 W \delta\eta \qquad (\text{since } \lambda = W\delta\eta) \\ &= \delta\eta^t S^t S \delta\eta \end{aligned}$$

where D is the diagonal matrix with entries the singular components and the superscript t denotes a transpose. Thus in the mean $H(g^* + \delta g^*) \approx H(g^*) + \delta\eta^t F \delta\eta$ where $F = S^t S$ is the Fisher Information Matrix.

8 SOFTWARE

A Matlab software package has been written to perform the analyses presented in the main paper. This will be available from http://wsbc.warwick.ac.uk/www/. The package requires Matlab 7.

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